5-Substituted Uracils (1)

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The historical method of choice for the preparation of 5-substituted uracils has been that of direct synthesis. For example, one might consider the condensation of β-methylmalic acid with urea affording thymine (2). Many variants are known including the use of α-substituted ethoxymethylene acetic acid derivatives (3).

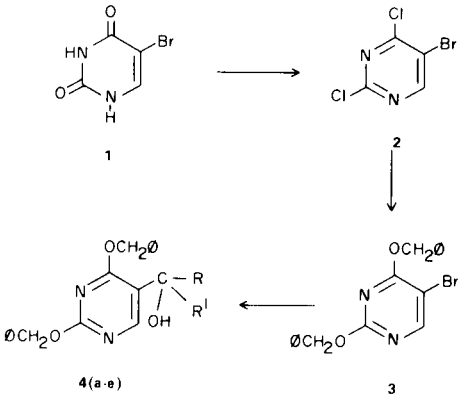
It was of interest to us to synthesize several uracil derivatives having relatively long chain groups in position five. Conventional procedures did not suffice in these instances. For example, the base catalyzed condensation of methyl isovalerate with methyl formate was unsuccessful. Attempts at formylating ethyl 5-methyl hexanoate were also failures. To obviate these difficulties, an alternate sequence to these uracil derivatives has been developed.

Five-bromouracil (**1**) (4a-b) was conveniently converted to 2,4-dichloro-5-bromopyrimidine (**2**) (4a-b), which in turn was readily converted to 2,4-dibenzyloxy-5-bromopyrimidine (**3**) with sodium benzyloxide in benzyl alcohol. Pyrimidine **3** was then converted at -85° to the corresponding 5-lithio derivative with *n*-butyllithium, which was immediately condensed with appropriate aliphatic carbonyl compounds (5) to afford the carbinols **4(a-e)** having the desired carbon skeleton at C-5. This procedure is a minor variation of that of Binkley and coworkers (6a-b) who synthesized 5-acyl and pseudouridine analogues in a similar fashion at -70°. In our hands, however, no product could be obtained at -70° and only at or below -85° could good yields be realized. These transformations are depicted below and summarized in Table I.

TABLE I

4	R	R^1	M.p., °C	% Yd.
a	CH_3-	CH_3-	81-82	41.8
b	H-	$(CH_3)_2CH$-	92-93	76.6
c	H-	ϕ-CH_2-	76-79	49.8
d	H-	$(CH_3)_2CH$-CH_2CH_2-	74-76	55.0
e	H-	$(CH_3)_2CH$-$(CH_2)_3$-	81-84	51.8

Since it was also of interest to us to prepare the corresponding saturated side chain compounds in position five, the catalytic hydrogenation behavior of carbinols **4(a-e)** was examined. Two equivalents hydrogen were rapidly consumed at 25° under 3 atmospheres pressure. To effect hydrogenolysis of the carbinol in position 5, heating to 100° was necessary and longer reaction times were required. If the reductions were stopped after consumption of two equivalents of hydrogen, good yields of the debenzylated carbinols could be obtained. In the case of **4a**, no intermediate debenzylated carbinol could be isolated. When a reduction of **4a** was halted after consumption of one equivalent of hydrogen, nmr analysis of the reaction mixture indicated that the tertiary alcohol in **4a** was eliminating water initially, and then undergoing reduction. This elimination is not surprising since the reductions were run in glacial acetic acid. These transformations are illustrated below and summarized in Tables II and III.



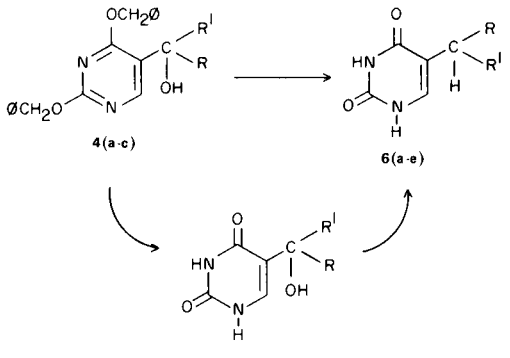


TABLE II

5(a)	R	R^1	M.p., °C	% Yd.
b	H-	$(CH_3)_2CH$-	dec. >200	55.5
c	H-	ϕCH_2-	dec. >212	48
d	H-	$(CH_3)_2CH\text{-}CH_2CH_2$-	dec. >250	56.9

(a) Derivative **e** was never prepared due to a scarcity of **4(e)**.

TABLE III

6	R	R^1	M.p., °C	% Yd. (a)
a	CH_3-	CH_3-	283-284	50
b	H-	$(CH_3)_2CH$-	296-298	53.5
c	H-	ϕCH_2-	280-282	41.5
d	H-	$(CH_3)_2CH\text{-}CH_2\text{-}CH_2$-	271-273	88
e	H-	$(CH_3)_2CH(CH_2)_3$-	268-269	84

(a) Through yields from **4**.

As would be expected, the isolated debenzylated carbinols **5(b-d)** were readily converted to the alkyl uracils **6(b-e)** under the reduction reaction conditions.

Further investigation of condensations of pyrimidyl lithium compounds is under way and will be reported at a later date.

EXPERIMENTAL

5-Bromo-2,4-dichloropyrimidine (**2**).

A mixture of 210.8 g. (1.049 moles) of 5-bromouracil (**1**); 253.8 g. (1.21 moles) of phosphorus pentachloride and 825 ml. (8.99 moles) of phosphorus oxychloride was refluxed for 41 hours. The excess phosphorus oxychloride was removed under vacuum and the residue flushed with xylene (2 x 200 ml.), cooled and quenched in 1500 ml. of ice water. After the addition of 1500 ml. of ether the mixture was stirred for 20 minutes and the layers were then separated. The aqueous layer was further extracted with ether (2 x 500 ml.) and the combined ether layers were washed with water (2 x 1 l.), 5% aqueous sodium bicarbonate solution (1 x 1 l.) and after a final water wash (1 l.), dried over magnesium sulfate. The ether was concentrated *in vacuo* and the resultant oil purified by fractional distillation to give 216.2 g. (90.7%) of 5-bromo-2,4-dichloropyrimidine (**2**); b.p., 77.5°/1.3 mm.

5-Bromo-2,4-dibenzyloxypyrimidine (**3**).

To 290 ml. of benzyl alcohol contained in a 1-l. round-bottomed flask was added 10.7 g. (0.465 g.-atom) of sodium. The formation of the sodium salt was facilitated by heating to 135°. The solution was cooled in an ice bath and 40.7 g. (0.178 mole) of 5-bromo-2,4-dichloropyrimidine (**2**) was added at 10-15° over a 1 hour period. After stirring overnight at room temperature, 290 ml. of tetrahydrofuran was added, the mixture stirred an additional 20 minutes and then filtered. The filtrate was concentrated *in vacuo*.

It should be noted that in order to avoid decomposition during the removal of the benzyl alcohol the temperature should not exceed 125°. The residue was dissolved in hot heptane, filtered and the filtrate cooled in an ice bath for 1-2 hours with stirring. The solids were filtered off, washed with ether and dried at room temperature overnight under vacuum. A total of 57 g. (86.1%) of **3** was obtained, m.p. 86-88°.

2,4-Dibenzyloxy-5-(α,α-dimethyl)pyrimidinemethanol (**4a**).

To a stirred solution of 92 g. (0.248 mole) of 5-bromo-2,4-dibenzyloxypyrimidine (**3**) in 1530 ml. of dry tetrahydrofuran, cooled to -95° in a liquid nitrogen bath, was added in an atmosphere of dry nitrogen 209 ml. (0.428 mole) of a 2.05 *M* solution of *n*-butyllithium in hexane. The reaction mixture was stirred for 3 minutes and 31.13 g. (0.536 mole) of anhydrous acetone was added at such a rate as to maintain the temperature below -80°. The solution was stirred for several minutes at -80° and then allowed to warm to 0° at which point it was acidified to *p*H ~2 with dilute hydrochloric acid (~ 2*N*). After the addition of 300 ml. of water, at 0-5°, the layers were separated and the aqueous layer extracted with ether (2 x 300 ml.). The combined organic layers were dried over mangesium sulfate, filtered, and the filtrate concentrated *in vacuo* to give 93.7 g. of crude **4a**. The crude oil was chromatographed on 1200 g. of silica, eluted with chloroform/ether (4:1) to afford 36.4 g. (41.8%) of the alcohol **4a** which crystallized on standing, m.p. 81-82°. After an 1800 ml. forerun, the product was eluted in fractions 18-25 (200 ml. each).

Anal. Calcd. for $C_{21}H_{22}N_2O_3$ (350.4): C, 71.98; H, 6.33; N, 7.99. Found: C, 71.83; H, 6.31; N, 7.90.

5-Isopropyluracil (**6a**).

A mixture of 36.4 g. (0.104 mole) of the intermediate alcohol **4a** in 500 ml. of glacial acetic acid, and 7.5 g. of 5% palladium on charcoal was shaken under 40 psi hydrogen gas pressure at room temperature for approximately 20 minutes. After the initial uptake ceased, denoting removal of the benzyloxy groups, the reaction mixture was heated at 50° for 4 hours at which time the hydrogen uptake amounted to 93% of the theoretical. The reaction mixture was filtered and the cake washed with several portions of glacial acetic acid. The combined filtrate and washes were concentrated to dryness *in vacuo* and the crude solid triturated with 150 ml. of ether. Recrystallization from 1300 ml. of hot ethanol gave 8 g. (50%) of analytically pure 5-isopropyluracil (**6a**), m.p. 283-284°. The above product was combined with 7 g. of equivalent material and all physical and analytical data were made on the blend.

Anal. Calcd. for $C_7H_{10}N_2O_2$ (154.177): C, 54.52; H, 6.52; N, 18.17. Found: C, 54.50; H, 6.47; N, 18.04.

2,4-Dibenzyloxy-5-(α-isopropyl)pyrimidine-(*R,S*)-methanol (**4b**).

n-Butyllithium (0.0336 mole) (16.4 ml. of a 2.05*M* solution in hexane) was added under a nitrogen atmosphere to a solution of 7.2 g. (0.0194 mole) of 5-bromo-2,4-dibenzyloxypyrimidine (**3**) in 120 ml. of dry tetrahydrofuran precooled to -90° in a liquid nitrogen bath. After addition was completed (~ 20 minutes) the solution was stirred for 2-3 minutes and then 3.81 ml. (0.042 mole) of isobutyraldehyde was rapidly added, the temperature being maintained below -80°. The reaction mixture was then allowed to reach 0°. The *p*H was adjusted to 2-3 with 2*N* hydrochloric acid and 20 ml. of water was added dropwise at 0-5°. The layers were separated, the aqueous layer extracted with ether (2 x 25 ml.) and the combined organic layers dried over magnesium sulfate. After filtration the reaction mixture was concentrated *in vacuo* to a viscous oil which partially solidified

upon standing. The waxy solid was dissolved in approximately 200 ml. of warm hexane, cooled, and the solids filtered off, washed once with hexane and then with several portions of petroleum ether. A total of 5.4 g. (76.6%) of **4b**, m.p. 92-93° was obtained after drying 18 hours/50°/1 mm.

Anal. Calcd. for $C_{22}H_{24}N_2O_3$ (364.4): C, 72.45; H, 6.64; N, 7.69. Found: C, 72.15; H, 6.37; N, 7.50.

2,4-Dihydroxy-5-(α-isopropyl)pyrimidine-(*R,S*)-methanol (**5b**).

A mixture of 5 g. (0.0137 mole) of the intermediate alcohol **4b**; 75 ml. of glacial acetic acid and 0.5 g. of 5% palladium on charcoal was shaken under 40 psi hydrogen gas pressure at room temperature for ½ hour whereby two equivalents of hydrogen were taken up. The reaction mixture was filtered and the cake washed with several portions of glacial acetic acid. The combined filtrate and washes were concentrated to dryness *in vacuo* and the crude solid recrystallized from 50 ml. of water to give 1.4 g. (55.5%) of 2,4-dihydroxy-5-(α-isopropyl)pyrimidine-(*R,S*)-methanol (**5b**); m.p. >200° dec.

Anal. Calcd. for $C_8H_{12}N_2O_3$ (184.21): C, 52.17; H, 6.57; N, 15.21. Found: C, 52.03; H, 6.47; N, 14.94.

5-(2-Methylpropyl)uracil (**6b**).

A mixture of 58.1 g. (0.159 mole) of 2,4-dibenzyloxy-5-(α-isopropyl)pyrimidine-(*R,S*)-methanol (**4b**), 5 g. of 5% palladium on charcoal and 750 ml. of glacial acetic acid was shaken at 40 psi hydrogen gas pressure at room temperature. After two equivalents of hydrogen were taken up, an additional 5 g. of catalyst and 750 ml. of ethanol were added and the mixture heated at 80-100° under hydrogen gas pressure until uptake of hydrogen ceased (completion confirmed by tlc); approximate heating time 8 hours. The hot reaction mixture was filtered and the residue washed with several portions of hot glacial acetic acid. The combined filtrate and washes were concentrated *in vacuo* and the resultant solid triturated with ether. After air drying the crude product (23.4 g.) was dissolved in 90 ml. of 2.5*N* sodium hydroxide, treated with 1 g. of Darco KB, filtered, and the filtrate acidified (~ *p*H 2) with 2*N* hydrochloric acid. The product was filtered off, washed with 3 x 100 ml. cold water and dried 18 hours/80°/0.1 mm.; yield 14.35 g. (53.5%). The above 14.35 g. was combined with 4.9 g. of equivalent material from another run and the 19.25 g. of **6b** was further purified, following the procedure described above, to give 17.8 g. of 5-(2-methylpropyl)-uracil (**6b**) after drying; m.p. 296-298° dec.

Anal. Calcd. for $C_8H_{12}N_2O_2$ (168.21): C, 57.14; H, 7.19; N, 16.66. Found: C, 57.05; H, 7.08; N, 16.44.

2,5-Dibenzyloxy-5-(α-benzyl)pyrimidine-(*R,S*)-methanol (**4c**).

To a stirred solution of 114 g. (0.308 mole) of 2,4-dibenzyloxy-5-bromopyrimidine (**3**) in 1900 ml. of dry tetrahydrofuran, cooled to -95° in a liquid nitrogen bath, was added in an atmosphere of dry nitrogen 170 ml. (0.338 mole) of a 2.38*M* solution of *n*-butyllithium in hexane. The reaction mixture was stirred for 3 minutes and 80 ml. (0.65 mole) of freshly distilled phenylacetaldehyde was introduced at such a rate that the temperature did not exceed -80°. The solution was stirred several minutes at -80° and was then allowed to slowly reach 0°, at which point it was acidified with 225 ml. of 2.5*N* hydrochloric acid. After the addition of 250 ml. of cold water at 0-10°, the layers were separated and the aqueous layer extracted with ether (3 x 200 ml.). The combined organic layers were dried over magnesium sulfate, filtered, and the filtrate concentrated *in vacuo* to give 77 g. of crude **4c**. The crude oil was taken up in 1500 ml. hot cyclohexane and allowed to slowly cool. The resulting crystalline precipitate was isolated, washed with 50 ml. fresh cyclohexane and vacuum dried at 50° and 1 mm. to afford 45.9 g. of **4c**, m.p. 76-79°. A second crop of 16.5 g., m.p. 76-79° could be obtained by concentration of the first crop mother liquor by 50% and recooling. The total yield was 62.4 g. (49.8%).

Anal. Calcd. for $C_{26}H_{24}N_2O_3$: C, 75.72; H, 5.86; N, 6.79. Found: C, 76.00; H, 6.21; N, 6.47.

5-(α-Hydroxyphenethyl)uracil (**5c**).

A mixture of 22.2 g. (0.054 mole) of 2,4-dibenzyloxy-5-(α-benzyl)pyrimidine-(*R,S*)-methanol (**4c**); 300 ml. of glacial acetic acid and 3 g. of 10% palladium on carbon was shaken under 40 psi hydrogen gas pressure at room temperature for approximately 1 hour during which time two equivalents of hydrogen were taken up. The reaction mixture was filtered and the cake washed with several portions of glacial acetic acid. The combined filtrate and washes were concentrated *in vacuo*; the residue triturated with 3 x 25 ml. of ether and the crude solids recrystallized from 1 l. of hot water. The 6 g. (48%) of **5c** thus obtained was combined with 22 g. of equivalent material, recrystallized from 5 l. of water and the solids, dried 18 hours/80°/0.1 mm. to give 16.7 g. of pure 5-(α-hydroxyphenethyl)uracil (**5c**), m.p. 212° dec.

Anal. Calcd. for $C_{12}H_{12}N_2O_3$ (232.25): C, 62.04; H, 5.21; N, 12.07. Found: C, 61.87; H, 5.11; N, 11.80.

5-(β-Phenethyl)uracil (**6c**).

A mixture of 31.78 g. (0.077 mole) of the intermediate alcohol **4c**, 450 ml. of glacial acetic acid and 4.5 g. of 10% palladium on carbon was shaken under 40 psi hydrogen gas pressure at room temperature until the initial uptake ceased. The mixture was heated for several hours at 100° until there was no further uptake. The hot reaction mixture was filtered through a Celite cake and the cake washed with several portions of hot glacial acetic acid. The combined filtrate and washes were concentrated to an approximate volume of 150 ml. and then chilled. The solids were filtered off, washed with ether and dried to give 6.9 g. (41.5%) of crude 5-(β-phenethyl)uracil (**6c**). A total of 13.6 g. of the product was recrystallized from 5 l. of methanol to afford 7.6 g. of **6c**. A second crop was obtained by concentrating the methanol mother liquors to one half volume, chilling and filtering off the product. The combined crops, after drying 18 hours/80°/0.1 mm., gave 10.4 g. of analytically pure 5-(β-phenethyl)uracil (**6c**), m.p. 280-282°.

Anal. Calcd. for $C_{12}H_{12}N_2O_2$ (216.25): C, 66.64; H, 5.61; N, 12.96. Found: C, 66.38; H, 5.88; N, 12.78.

4-Methylpentanal.

To 16.0 g. (0.66 mole) of magnesium turnings in 50 ml. of anhydrous diethyl ether was added a few crystals of iodine. Then, under a nitrogen atmosphere, 100.5 g. (0.66 mole) of isoamyl bromide in 150 ml. anhydrous diethyl ether was added dropwise with stirring at such a rate that a gentle reflux was maintained. When the addition was completed, the reaction mixture was allowed to stir at room temperature overnight (~ 16 hours). The reaction mixture was treated with 99.5 g. (0.66 mole) of triethyl orthoformate in 50 ml. of diethyl ether at such a rate that a gentle reflux was maintained (initial warming was usually required). The reaction mixture was refluxed with stirring for 2 hours after which volatiles were distilled off to a vapor temperature of 70°, and the mixture was cooled to 15° and 200 ml. of ice water introduced. The solid mass was crushed up with a stirring rod, 150 ml. of ether added, and the insolubles filtered off. The layers were separated and the aqueous phase reextracted with 100 ml. of ether. The combined ether extracts were dried over magnesium sulfate, filtered, and concentrated *in vacuo* (rotary evaporator,

T ≤ 40°) to a tan oil, 94 g. This crude acetal was used without further purification as follows. To 300 ml. of 3*N* sulfuric acid was added 94 g. (0.54 mole) of crude acetal and the mixture refluxed with stirring for 2 hours. The mixture was steam distilled to a vapor temperature of 100°, affording 37.8 g. (70%) of crude aldehyde that had a glc purity of 91.1%. This material was satisfactory to use in the subsequent condensation providing that it was well dried over molecular sieves first. It may be mentioned that if one precipitates the aldehyde as its sodium bisulfite addition product and after isolation decomposes the adduct with aqueous base one can obtain aldehyde of 95.5% purity by steam distillation.

2,4-Dibenzyloxy-5-(α-isoamyl)pyrimidine-(*R,S*)-methanol (**4d**).

To a solution of 68.5 g. (0.185 mole) of 5-bromo-2,4-dibenzyloxypyrimidine (**3**) in 1138 ml. of tetrahydrofuran (dried over magnesium sulfate) cooled to -95° in a liquid nitrogen bath, was added, under a nitrogen atmosphere, 0.203 mole of *n*-butyllithium (85.3 ml. of a 2.38*M* solution in hexane). After addition was completed (in 10 minutes) the solution was stirred for 2-3 minutes and the 39.8 g. (0.398) of freshly steam distilled and molecular sieve dried 4-methylpentanal was rapidly added, the temperature being maintained at -90°. The reaction mixture was allowed to reach 0°; the *p*H adjusted to *ca.* 2 with 130 ml. of 2.5*N* hydrochloric acid, and 200 ml. of ice water then added dropwise at 0-5°. The layers were separated, the aqueous layer extracted with 3 x 150 ml. of ether and the combined organic layers dried over magnesium sulfate. After filtration, the filtrate was concentrated *in vacuo* to a viscous oil which was dissolved in 150 ml. of hot hexane and allowed to stand overnight at room temperature. The crude solids (21.5 g.) were filtered off, washed with several portions of hexane and dried *in vacuo* at room temperature. An additional 12.76 g. of **4d** was obtained from the hexane mother liquors, in two crops for a total yield of 34.29 g. (55%), m.p. 74-76°. The combined product exhibited one spot on tlc R_f 0.32 (Analtec Silica gel HF: chloroform/ether (4:1)) and was used in the next step without further purification.

Anal. Calcd. for $C_{24}H_{28}N_2O_3$ (392.5): C, 73.45; H, 7.19; N, 7.14. Found: C, 73.17; H, 7.09; N, 7.05.

2,4-Dihydroxy-5-(α-isoamyl)pyrimidine-(*R,S*)-methanol (**5d**).

A mixture of 4.55 g. (0.0116 mole) of the benzylated alcohol **4d**; 150 ml. of glacial acetic acid, and 1.0 g. of 5% palladium on charcoal was shaken at room temperature under 40 psi hydrogen gas pressure. After approximately 45 minutes, two equivalents of hydrogen were taken up. The reaction mixture was filtered; the cake washed with several portions of glacial acetic acid, and the combined filtrate and washes concentrated to dryness *in vacuo*. The crude solid was triturated with 2 x 25 ml. of ether and air dried; yield 2.2 g. After two recrystallizations from water 100 ml./g., 10% Darco KB, 1.4 g. (56.9%) of analytically pure 2,4-dihydroxy-5-(α-isoamyl)pyrimidine-(*R,S*)-methanol (**5d**) was obtained, m.p. >250° dec. (sinters at 202°).

Anal. Calcd. for $C_{10}H_{16}N_2O_3$ (212.26): C, 56.58; H, 7.60; N, 13.21. Found: C, 56.59; H, 7.72; N, 13.01.

5-(4-Methylpentyl)uracil (**6d**).

A mixture of 21.5 g. (0.0549 mole) of the intermediate alcohol **4d** in 750 ml. of glacial acetic acid, and 5 g. of 5% palladium on charcoal was shaken under 40 psi hydrogen gas pressure at room temperature for approximately 1½ hours, at which time the initial uptake ceased. The reaction mixture was then heated at 100° for 2 hours; hydrogen uptake 100%+ of the theoretical. The reaction mixture was filtered hot (65°) and the insolubles washed with 2 x 50 ml. of hot glacial acetic acid. The combined filtrates were evaporated *in vacuo* leaving a near colorless solid. This solid was triturated with 35 ml. of ether and vacuum dried (24 hours, 60°, 10 mm.) to afford 9.5 g. (88%) of crude **6d**. A blend of several batches were recrystallized from methanol, yielding 9.2 g. (three crops) of colorless needles, m.p. 271-273°.

Anal. Calcd. for $C_{10}H_{16}N_2O_2$ (196.2): C, 61.21; H, 8.20; N, 14.26. Found: C, 60.92; H, 8.42; N, 14.13.

1-Bromo-4-methylpentane.

A mixture of 100 g. (0.99 mole) of 4-methyl-1-pentanol, 500 g. of 48% hydrobromic acid and 131 ml. of concentrated sulfuric acid was heated in a glass-lined bomb for 6 hours at 150°. The reaction mixture was cooled, quenched in 1.5 l. of ice water and filtered. The filtrate was extracted with ether (4 x 500 ml.), the combined ether extracts washed once with 300 ml. of water and then dried over anhydrous magnesium sulfate. After filtration, the ether was removed by distillation at atmospheric pressure and the crude residue (164.8 g.) distilled at 47-49°/20 mm. to afford 114.9 g. (70%) of pure (by gas chromatography) 1-bromo-4-methylpentane n_D^{20} = 1.4400 (lit., (6) n_D^{20} = 1.44897).

5-Methylhexanal Diethyl Acetal.

To 15.5 g. (0.636 mole) of magnesium turnings and 500 ml. of anhydrous ether (dried over molecular sieves) contained in a 2-l. round-bottomed flask, under a nitrogen atmosphere, was added a solution of 105 g. (0.636 mole) of 1-bromo-4-methylpentane in 100 ml. of ether at a rate sufficient to maintain a gentle reflux. After addition was completed, the mixture was refluxed an additional hour, cooled to room temperature and 95 g. (0.65 m.) of ethyl orthoformate, dried over molecular sieves) introduced over a 20 minute period. The mixture was refluxed for 4 hours and then stirred overnight at room temperature. The bulk of the ether was removed by distillation at atmospheric pressure and the resultant slurry cooled in an ice bath. Two hundred milliliters of saturated aqueous ammonium chloride solution was added dropwise, followed by 450 ml. of water and the mixture stirred overnight at room temperature. The reaction mixture was filtered and upon standing separated into two layers, the upper oily layer of acetal (102.2 g.) was then decanted off. An additional 9.8 g. of acetal was obtained by extracting the aqueous phase with ether (3 x 300 ml.); the combined extracts being dried over anhydrous magnesium sulfate and concentrated *in vacuo* at room temperature. The acetal, 112 g., was distilled through a 6 inch Vigreux column, the main fraction (b.p., 73.5-76°/9-10 mm.) was combined with an earlier cut of 14.5 g. (b.p., 66-79°/13 mm.) and the total redistilled. The second distillation yielded 73.4 g. (61%) of 5-methylhexanal diethyl acetal, b.p., 70-75°/8-9 mm., n_D^{20} = 1.4090 (lit., (8) b.p., 170°/745 mm.).

5-Methylhexanal.

A mixture of 47.5 g. (0.253 mole) of the intermediate acetal and 200 ml. of 3*N* sulfuric acid was distilled to a vapor temperature of 100°. The organic phase was separated, dried over magnesium sulfate and filtered yielding 21.1 g. (73.5%) of aldehyde 89.7% purity by gas chromatography. This material was combined with 5.45 g. of aldehyde obtained in a previous run and the 26.55 g. distilled at 29-32°/9.5 mm., yield 16.05 g., n_D^{20} = 1.4060 (lit., (9) n_D^{20} = 1.4114). A total of 38 g. of single peak 5-methylhexanal was prepared.

2,4-Dibenzyloxy-5-(α-4-methylpentyl)pyrimidine-(*R,S*)-methanol (**4e**).

A solution of 56.4 g. (0.152 mole) of 5-bromo-2,4-dibenzyl-

oxypyrimidine (**3**) in 900 ml. of anhydrous tetrahydrofuran (dried over magnesium sulfate) was cooled to -95° in a liquid nitrogen bath and 0.167 mole of *n*-butyllithium (2.5*M* solution in hexane) was added over a 5 minute period under a nitrogen atmosphere. The solution was aged 3 minutes and 38 g. (0.334 mole) of 5-methylhexanal was added as rapidly as possible at -95° to -90°. The cooling bath was lowered and the reaction mixture allowed to reach 0°, the *p*H adjusted by the dropwise addition of 90 ml. of 2.5*N* hydrochloric acid and 150 ml. of ice water then added at 5-10°. The layers were separated the aqueous phase extracted with 3 x 90 ml. portions of ether and the combined organic layers dried over anhydrous magnesium sulfate. After filtration, the filtrate was concentrated *in vacuo* to a viscous oil which was dissolved in approximately 150 ml. of hot hexane, filtered, and the filtrate cooled slowly. The white crystalline solids were filtered off, washed once with hexane and dried 18 hours/45°/0.1 mm. to give 29.4 g. of **4e**; m.p., 81-84°. An additional 2.7 g. of **4e** was obtained from the hexane mother liquors after cooling overnight at 5° (51.8%).

Anal. Calcd. for $C_{25}H_{30}N_2O_3$ (406.5): C, 73.86; H, 7.44; N, 6.89. Found: C, 73.59; H, 7.03; N, 7.07.

5-(5-Methylhexyl)uracil (**6e**).

A mixture of 29.4 g. (0.0724 mole) of the intermediate alcohol **4e**, 500 ml. of glacial acetic acid (Merck reagent) and 5 g. of 5% palladium on carbon was shaken under 40 psi hydrogen gas pressure at room temperature until the initial uptake ceased (*ca.* 30 minutes). The mixture was then heated at 100° until there was no further uptake (several hours). The reaction mixture was filtered hot and the cake washed with several portions of hot glacial acetic acid. The combined filtrate and washes were concentrated *in vacuo*, the crude solid triturated with 150 ml. of ether and dried in a moisture teller at 60°. The crude 5-(5-methylhexyl)-uracil (**6e**) (14.6 g.) was dissolved in approximately 150 ml. of warm (50°) 2.5*N* sodium hydroxide, filtered warm, and the product precipitated by the addition of 25 ml. of concentrated hydrochloric acid. The solids were filtered off, washed with 3 x 50 ml. of water; 1 x 40 ml. of ethanol, 3 x 50 ml. of ether and vacuum dried (18 hours/80°/0.1 mm.) to give 12.8 g. (84%) of analytically pure 5-(5-methylhexyl)uracil (**6e**), m.p. 268-269° dec.

Anal. Calcd. for $C_{11}H_{18}N_2O_2$ (210.28): C, 62.83; H, 8.63; N, 13.33. Found: C, 62.76; H, 8.61; N, 13.35.

REFERENCES

(1) Supported by Contract NIH 72-2002 from Chemotherapy, National Cancer Institute, National Institutes of Health.

(2) H. W. Scherp, *J. Am. Chem. Soc.*, **68**, 912 (1946).

(3) G. Shaw and R. N. Warrener, *J. Chem. Soc.*, 1958, 153.

(4a) G. E. Hilbert and E. F. Jansen, *J. Am. Chem. Soc.*, **56**, 134 (1954); (b) C. C. Cheng *et al.*, *ibid.*, **86**, 1869 (1964).

(5) Two of the carbonyl compounds employed, 4-methylpentanal and 5-methyl-hexanal required synthesis. The excellent procedure of Wood and Couley, *J. Soc. Chem. Ind.*, **42**, 429T (1923) was employed.

(6a) W. Asbun and S. B. Binkley, *J. Org. Chem.*, **31**, 2215 (1966). (b) T. V. Rajkunav and S. B. Binkley, *J. Med. Chem.*, **6**, 550 (1963).

(7) A. Buelens, *Rec. Trav. Chim.*, **28**, 119 (1909).

(8) S. Blake and G. Jones, *J. Chem. Soc.*, 430 (1963).

(9) A. L. Henne and P. Hill, *J. Am. Chem. Soc.*, **65**, 752 (1943).